

<https://helda.helsinki.fi>

Fetal programming of neuropsychiatric disorders by maternal pregnancy depression: a systematic mini review

Robinson, Rachel

2019-01

Robinson , R , Lahti-Pulkkinen , M , Heinonen , K , Reynolds , R M & Räikkönen , K 2019 , ' Fetal programming of neuropsychiatric disorders by maternal pregnancy depression: a systematic mini review ' , Pediatric Research , vol. 85 , no. 2 , pp. 134-145 . <https://doi.org/10.1038/s41390-018-0173-y>

<http://hdl.handle.net/10138/309434>

<https://doi.org/10.1038/s41390-018-0173-y>

unspecified

acceptedVersion

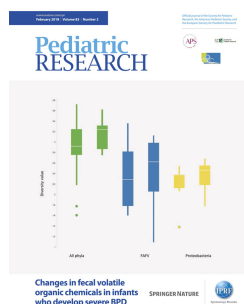
Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

Author Version: Published ahead of online first



Fetal programming of neuropsychiatric disorders by maternal pregnancy depression: A systematic mini review

Rachel Robinson, Marius Lahti-Pulkkinen, Kati Heinonen, Rebecca M Reynolds, Katri Räikkönen

Cite this article as: Rachel Robinson, Marius Lahti-Pulkkinen, Kati Heinonen, Rebecca M Reynolds and Katri Räikkönen, Fetal programming of neuropsychiatric disorders by maternal pregnancy depression: A systematic mini review, *Pediatric Research* _#####_ doi:10.1038/s41390-018-0173-y

This is a PDF file of an unedited peer-reviewed manuscript that has been accepted for publication. Springer Nature are providing this early version of the manuscript as a service to our customers. The manuscript will undergo copyediting, typesetting and a proof review before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers apply.

Review: Depression & Offspring

Fetal programming of neuropsychiatric disorders by maternal pregnancy depression: A systematic mini review

Rachel Robinson¹, Marius Lahti-Pulkkinen¹⁻³, Kati Heinonen¹, Rebecca M Reynolds², Katri Räikkönen¹

¹Department of Psychology and Logopedics, University of Helsinki, Helsinki, Finland

²University/British Heart Foundation Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

³National Institute for Health and Welfare, Helsinki, Finland

Corresponding Author:

Rachel K. Robinson

University of Helsinki, Meilahti

Medicum, Haartman Institute, E219

Haartmaninkatu 3, FI-00290 Helsinki

Rachel.robinson@helsinki.fi

(Phone) +358456421030

FINANCIAL STATEMENT: Funding for this review comes from an Academy of Finland Program Grant, European Commission Horizon 2020 Award SC1-2016-RTD-733280 for RECAP, European Commission Dynamics of Inequality Across the Life-course: structures and processes(DIAL) No 724363 for PremLife, and the Signe and Ane Gyllenberg Foundation.

DISCLOSURE STATEMENT: The authors declare no conflicts of interest.

CATEGORY/TYPE: Systematic Review

Abstract

BACKGROUND: Maternal depression complicates a large proportion of pregnancies. Current evidence shows numerous harmful effects on the offspring. Reviews, which include depression, concluded that stress has harmful effects on the offspring's outcomes neuro-cognitive development, temperament traits and mental disorders.

OBJECTIVE: This mini review of recent studies, sought to narrow the scope of exposure and identify studies specifically assessing prenatal depression and offspring neuropsychiatric outcomes.

STUDY ELIGIBILITY CRITERIA: The review included longitudinal, cohort, cross-sectional, clinical, quasi-experimental, epidemiological or intervention study designs published in English from 2014-2018.

PARTICIPANTS: Study populations included mother-child dyads, mother-father-child triads, mother-alternative caregiver-child triads and family studies utilizing sibling comparisons.

METHODS: We searched PubMed and Web of Science. Study inclusion and data extraction were based on standardized templates. The quality of evidence was assessed using the Newcastle-Ottawa Scale(NOS).

RESULTS: Thirteen studies examining neuropsychiatric outcomes were included. We judged the evidence to be moderate to high quality.

CONCLUSIONS: Our review supports that maternal prenatal depression is associated with neuropsychiatric adversities in children.

Review: Depression & Offspring

IMPLICATIONS: Future investigations should unravel the biological underpinnings and target timely interventions as early in pregnancy as possible to prevent offspring neuropsychiatric harms.

Author accepted manuscript

Introduction

Early life environmental adversities may exert consequences upon developing cells, tissues, and organs, their structure and function. These biological alterations may result in phenotypic differences between individuals that persist throughout the lifespan – a developmental plasticity phenomenon called ‘prenatal programming’(1–4).

Maternal depression complicates a large proportion of pregnancies with 7.4%-20% of women experiencing major or minor depression, dysthymia or clinically significant depressive symptomatology during pregnancy(5). Yet, a large proportion of pregnant women with depression remain undetected(6). This does not merely reflect a lack of systematic screening, but also an unwillingness of women to admit experiencing depressive symptoms(7). Nearly half of women reported feeling too embarrassed to confess to a healthcare professional that they are not feeling well and almost one-third were afraid that if they divulged their feelings, their baby would be taken away(7). Many of the rest feared repercussions such as stigma(7).

Due to the high prevalence, maternal depression is a major complication of pregnancy and childbirth. Strongly predicted by prenatal depression(8), maternal postpartum depression also carries adverse consequences for the offspring(9). One systematic review and meta-analysis of studies published between 2010-2015, concluded that offspring of women with untreated depression during pregnancy were 56% more likely to be born preterm(< 37 gestational weeks) and 96% more likely to be born with a low birth weight(< 2.5 kg)(10). Another review of studies published up to 2015 focused on the effects of maternal untreated pregnancy depression on a series of offspring outcomes ranging from birth outcomes and physiological effects to cognitive and psychopathological effects(11). While the evidence of the reviewed studies showed a

number of harmful effects on the offspring, yet the evidence was controversial, particularly regarding preterm birth and low birth weight(11). Pregnancy factors such as maternal age, gestation length, current maternal depressive status, pre-pregnancy obesity, gestational diabetes/hypertension, pre-eclampsia, and substance use during pregnancy, if not properly considered, may inflate the to the body of evidence. Yet, another recent review of studies published between 2010-2017 concluded that maternal stress in pregnancy, which included depression, has harmful effects on the offspring's neuro-cognitive development, negative affectivity, difficult temperament and mental health(2). As it is important to consider the alternative possibilities, numerous reviews explore the harmful effects of offspring exposure to pharmacologically treated(e.g. SSRIs) maternal prenatal depression(12–15).

To the best of our knowledge, no reviews have focused specifically on the consequences of prenatal depression on offspring neuropsychiatric outcomes. Hence, the objective of this review was to assess all recent studies assessing prenatal depression and offspring neuropsychiatric outcomes. We evaluate the quality of the evidence of the reviewed studies using the Newcastle-Ottawa Scale assessment(NOS). To deepen the discussion, we examine whether potential harmful effects of maternal depression on offspring neuropsychiatric outcomes are specific to the pregnancy period or explained by postnatal depression and whether a specific window of vulnerability exists when the effects of prenatal depression on offspring neuropsychiatric outcomes are most detrimental. Furthermore, we briefly explore the potential mechanisms through which prenatal depression may exert harmful consequences on offspring neuropsychiatric development. Lastly, we highlight treatment methods for prenatal depression, thereby possibly preventing offspring neurodevelopmental harm.

Methods

We searched Pubmed/MEDLINE and Web of Science databases for human longitudinal, cohort, and cross-sectional studies, published between January 2014 and February 2018 in English, with either clinical, quasi-experimental, epidemiological or intervention study designs.

We included studies focusing on mother-child dyads, mother-father/alternate caregiver-child triads. Study criteria included maternal prenatal depression with any depressive disorder diagnosis identified via medical registries, psychiatric interview, or depressive symptoms measured with self-report questionnaires. We excluded studies that used antidepressant use as the sole exposure measure, reported only on lifetime history of depression, used retrospective self-reports or unclearly defined exposure. We excluded studies that used other forms of psychological stress or only a combined exposure measure, such as a depression and anxiety mean score. For offspring neuropsychiatric outcomes, we considered internalizing and externalizing problems, including anxiety, depression, attention, conduct problems, Attention Deficit Hyperactivity Disorder(ADHD), autism spectrum disorders and schizophrenia.

We utilized RevMan5 software to generate the PRISMA flow diagram(16) that describes the study selection process(Figure 1). The studies' characteristics, participant demographics and data were systematically collected from each study using a standardized template.

We assessed risk of bias and the methodological quality in non-randomized, non-intervention, observational studies using NOS, a recommended method from the Cochrane Handbook of Systematic reviews(17,18).

Results

The sensitive search strategy applied produced 5712 articles(1083=Pubmed, 4629=Web of Science) for all studies up until February 2018. Refining the results to publications from 2014-

2018, rendered 766 articles(PubMed, n=135; Web of Science, n=631 for title and abstract review. Further hand searching of reference lists and other sources augmented the search findings(n=9). We included 13 empirical studies that examined prenatal depression and neuropsychiatric outcomes in offspring. See Figure 1 for the PRISMA diagram of inclusion.

Summary of Main Findings

Refer to Table 1 for a complete list of included studies, study characteristics and main findings, as well as each studies covariates.

A Finnish longitudinal cohort study by Korhonen et al.(21), among 192 mother-child dyads, found that prenatal depression was significantly associated with the 16-year-old child's externalizing behavior problems. Notably, in this study population, maternal depression, when the child was 8-9-years-old, was not significantly associated with the child's behavior problems, but when measured at the child's age of 16 years it was associated with the child's externalizing behavior problems(19). The study reported that children of women who had a 'high stable' trajectory of depressive symptoms from pregnancy to the child's adolescence had the highest risk for externalizing problems, suggesting that both pre-and-postnatal depression increase the child's risk(19).

The Finnish Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) study by Lahti et al.(15) of 2296 mother-child dyads found that higher maternal prenatal depressive symptoms were associated with higher internalizing, externalizing and total psychiatric problems of the child aged 1.9-5.9 years. These effects were independent of maternal depressive symptoms measured at the childhood follow-up, suggesting that the harmful effects on the child outcomes are specific to the prenatal period. The effects were gestation-week non-

specific, meaning that higher maternal depressive symptoms at the 14 biweekly measurements between 12-39 gestational weeks, were associated with more problems across a broad range of child behaviors(20). The study found that maternal depressive symptoms at the child follow-up partially mediated the prenatal depression effects. Additionally, the offspring of women who were consistently more depressed during pregnancy and at the childhood follow-up displayed the most problems(20), supporting the concept that both pre- and postnatal factors play a role.

In another study from the Finnish PREDO cohort by Woldford et al.(18), among 1779 mother-child dyads, higher maternal depressive symptoms during pregnancy were associated with significantly increased ADHD symptoms in children aged 3-6 years. These effects were independent of and partially mediated by maternal depressive symptoms measured in the childhood follow-up and were gestation-week non-specific; children of mothers with consistently high depressive symptoms both during pregnancy and in early childhood had the most ADHD symptoms (18).

The German Franconian Cognition and Emotion Study(FRANCES) study by Eicheler et al., which assessed children of 61 depressed and 143 non-depressed mothers, found that at age 6-9 years, offspring of depressed mothers scored higher on anxiety, depression and antisocial behavior(21). The associations with child depression and anxiety were independent of maternal depressive symptoms measured at the child follow-up, pointing to prenatal specificity of these effects(21). Yet, it remains unknown if the prenatal depression effects on child antisocial behavior would have been explained by maternal depressive symptoms during the child follow-up as the authors did not report these effects in the paper. This study also was unable to address if there would be a vulnerability window when maternal depressive symptoms would have had

the most harmful offspring consequences, as the study measured depressive symptoms only once, during the third pregnancy trimester(21).

In the Dutch Generation R study by El Marroun et al., among 5596 mother-child dyads, 1.5-6-year-old children exposed to maternal depressive symptoms (without SSRIs) at 20 weeks of gestation showed more pervasive developmental problems than the control group(22). These associations remained significant after adjusting for maternal postnatal depression. Supplemental analysis indicated that prenatal depressive symptoms tended to be associated with autistic traits even after adjusted for maternal depression at the child's age of 3 years(23). This study also measured affective problems and found an increased risk for affective problems in children who were exposed to prenatal maternal depression (without SSRIs)(23). With only one measure of prenatal depression, this study, however, leaves the vulnerability window unclear.

In the UK Avon Longitudinal Study of Parents and Children (ALSPAC) by Capron et al. among 4303 mother-child dyads, higher maternal depressive symptoms at 18th gestational week were associated with and increased risk for anxiety disorder in the 18-year-old offspring(25).

In another ALSPAC study by Leis et al. among 2891 mother-child dyads, higher maternal depressive symptoms at 18th and/or 32nd gestational weeks were associated with higher risk of hyperactivity, emotional symptoms, conduct problems and total difficulties in the 11-year-old offspring (26). When the child problems were rated by the child's teacher, maternal prenatal depressive symptoms remained a significant predictor of the child's hyperactivity(24).

In the third ALSPAC study by O'Donnell et al. among 7944 mother-child dyads, maternal depressive symptoms at 18 weeks gestation predicted consistently elevated levels of the child's behavior problems through ages 4 to 14 years(25).

All the ALSPAC study findings were independent of maternal postnatal depressive symptoms measured at the childhood follow-ups. While the ALSPAC study has maternal depressive symptoms measurements at 18th and 32nd gestational weeks, these are not systematically reported in the studies, hence leaving open the question of a window of vulnerability.

In another UK study by Plant et al., in the South London Child Development (SLCD) study of 103 mother-child dyads maternal depressive symptoms at 20 or 30 weeks of gestation were associated with an increased risk of depression in the 25-year-old offspring (26). In this study maternal prenatal depressive symptoms were correlated with maternal postnatal depressive symptoms measured up to 12 months after delivery. Yet, the postnatal depressive symptoms were not associated with the adult offspring depression. In contrast, children exposed to maternal depression in early childhood (1-6 years) were at an increased risk for adult depression (26). This study also revealed an additive effect where each additional exposure to maternal depression measured at different developmental stages increased the risk of depressive symptoms in the offspring in adulthood (26). This study concluded that childhood maltreatment mediated the effect of maternal prenatal depressive symptoms on the child's adulthood depression (28).

In another US longitudinal study of 196 young, low income, African American mothers and their children, a path analysis indicated two indirect paths mediating the effects of maternal prenatal depression on toddler total behavior problems (27). One indirect path indicated a significant path of maternal prenatal depression on toddler total problems at 24 months via maternal sensitivity at 24 months (27). The other indirect path showed that maternal depressive symptoms at 24 months mediated the effect of maternal prenatal depression on toddler total behavior problems at 24 months (27). It is unclear from this study whether prenatal depressive symptoms had effects on toddler behavior problems that were independent of maternal sensitivity and concurrent

depression. As this study measured maternal depressive symptoms only once during pregnancy, the study was not able to address the question of specific vulnerability window(27).

In another US study by Johnson, in a clinical subsample of 178 depressed mothers from the Emory Women's Mental Health Program for perinatal mental illness, 2.5-5-year-old children exposed to maternal pregnancy depression (without SSRI) were less likely to score in the 'at-risk range' for pervasive developmental disorder than those exposed to SSRI(28). The post hoc nested sibling analysis found that the decreased likelihood for pervasive developmental disorder in children with depressed mothers without SSRIs compared to those with SSRIs remained significant(28).

The US Californian registry study by Wieckowski et al., comprising nearly 9 million mother-child dyads, found that maternal major depressive disorder(MDD; recurrent and single episode), dysthymia, depressive disorder not otherwise specified, and bipolar disorder increased the 4-21-year-old offspring's risk of autism spectrum disorder by 1.6-2.75-fold(21). While the timing of the maternal hospitalizations during pregnancy and at delivery were available, the study did not report the associations separately by trimesters or delivery; nor reported data on maternal hospitalizations during the child follow-up period. Hence, it remains unclear if the effects were specific to the prenatal period and if effects varied according to pregnancy trimester.

Quality of the evidence

We found the overall quality of the evidence as high to moderate based on the NOS Assessment, which judged cohort and case-control studies on three domains; 1)selection, 2)comparability, and 3)outcome(Table 2 & Table 1).

The 13 prospective studies included in this review represent participants from 6 high income countries, 5 of which are European. The ALSPAC($n=3$)(1,24,29) and SLCD studies($n=1$)(26) both drew their cohorts from the southern UK population at around the same time-period. The PREDO($n=2$)(20,30), MoBA($n=1$)(31) and Korhonen et al.($n=1$)(19) studies examined Nordic populations. The German FRANCES(21) and the Dutch Generation R study(22) both examined southern European populations with Generation R comprising a multi-ethnic European population. In the US studies($n=3$)(27,28,32), however, the populations' distinct geographic, socioeconomic and clinical characteristics and ethnic variation, separate these three studies from each other.

All of the studies used mother-child dyads($n=14$), however, some studies used an additional caregiver measure(i.e. teacher or father)($n=3$)(22,24,29), or a sibling comparison model($n=2$)(28,31). Non-exposed participants were all drawn from the same populations as the exposed participants(1,19–22,24,26–32). Notably, there was one clinical subsample study(28). Only two studies used an objective maternal depression exposure measure, i.e. medical records diagnosis(32) and the Clinical Interview Schedule (CIS) structured interview(26). Nine of the other studies used validated maternal report measures such as the Center for Epidemiological Studies Depression Scale(CES-D)(20,27,30), Edinburgh Postnatal Depression Scale(EPDS)(19,21) for measuring prenatal depressive symptoms. The bi-weekly CES-D measurements in the PREDO on maternal prenatal depression sets a gold standard for understanding the stability and trajectory of symptoms throughout gestation and allows for time point vulnerability exploration(20,30), a key tenant missing from the other studies in this review. The ALSPAC study also measured maternal depression at multiple prenatal and postnatal timepoints with the EPDS, however, only selective timepoints were used in each of the studies' analyses(24–26,29).

The clinical subsample from the Emory Women's Mental Health Program measured exposure using self-reports of SRI use and the Beck Depression Inventory, 2nd Edition (BDI-II)(28). Although the BDI-II is a commonly used measure for depression in the general population, findings suggest questionable validity in prenatal and postnatal samples, especially when compared to the EPDS(33,34). The Norwegian MoBa study(31) used 3 selected items from the Symptoms Checklist(SCL) version 5 comprising an externally non-validated measure of maternal depressive symptoms(31). Internally, a Norwegian study reporting on the reliability and validity of the short form the psychometric measures used in the MoBA study, indicates a strong correlation between the 5 items in the SCL-8 short form and in 3 items in the SCL-5 with the original SCL-25 for depression(35). Authors, cited their previous work reporting a moderate level of agreement between the self-report and diagnostic interview measures, however using the 5-item version of the SCL-5(36).

For comparability, ten studies controlled for the sex of the offspring as the most important confounder(20–22,24–28,30,31), while three studies(19,29,32) did not control for sex, reducing comparability. All 13 studies controlled for at least one other important factor such as age, gestation length, current maternal depressive status, maternal pre-pregnancy obesity, gestational diabetes/hypertension, pre-eclampsia, smoking and alcohol use during pregnancy all of which may significantly impact the findings(See Table 1 for all covariates used in each analysis). Although one study, did not report any of the adjusted analysis in the paper, as the author's indicated that it had no effect on the results(21). Select studies accounted for novel confounders such as childhood maltreatment in path analysis which significantly attenuated the results(26), paternal pre and postnatal depression or sibling analysis(28,31), both of which account for genetic and environmental effects supporting the prenatal programming hypothesis. Yet,

regarding the sibling analyses, maternal depressive symptoms show high continuity from pregnancy to postpartum(16,27), and the Gjerde MoBA study(19) did not describe the level of differential exposure among siblings or the inter-correlations between antenatal and postpartum symptoms that would have been needed to assess whether multi-collinearity posed a concern for any analyses. Overall differences in adjustment for confounders decreased the comparability of the results across studies(19–22,24–32).

Regarding outcomes, 3 studies used an objective neuropsychiatric outcome measure removing the subjectivity of parental report questionnaires via medical records diagnosis (32), the Clinical Interview Schedule-Revised (CIS-R)(29) validated in young adult populations for identifying anxiety and depression (37), and the Structured Clinical Interview (26). All other studies (n=10) used mother/father/caregiver-rated questionnaires. Six studies used the Child Behavior Checklist(CBCL), which measures internalizing, externalizing and total problems, emotionally reactive, anxious/depressed, somatic, withdrawn, sleep, attention and aggressive behavior problems, and affective, anxiety, pervasive developmental, attention deficit/hyperactivity, and oppositional defiant problems alone(19,20,22,23,28,31) or in combination with the Youth Self Report(YSR)(19), or the Social Responsiveness Scale(22). Other studies measured parental reported symptoms using the Conners' Hyperactivity Index for ADHD(30), the Brief Infant-Toddler Social and Emotional Assessment (BITSEA), which assesses internalizing, externalizing, dysregulation and competence(27,38) and the SDQ for assessing prosocial behavior, hyperactivity, emotional symptoms, conduct problems, peer problems, and total difficulties(1,39). The FRANCES study measured internalizing and externalizing behaviors using a psychologist administered set of mother-rated questionnaires from the ICD-10 and DSM-

IV which are not well-known and are available only in the German language; hence it remains challenging to evaluate their reliability and validity(21) .

All 13 studies followed participants for a suitable length of time for the designated outcome of interest. Notably, however, the CBCL has only been validated for ages 1-5, and inclusion of some participants at age 6 could have impacted the results in the Generation R study (40% age 6)(22). Nine studies retained adequate numbers for follow-up and clarified how the authors dealt with missing data(19–22,26–28,30,31). Originally a very large cohort, the long term follow up of the ALSPAC studies(n=3)(1,24,29) experienced a high attrition rate, especially by follow up at 18 years(24,25,29). However, the long-term adulthood follow-up in the ALSPAC studies(24,25,29) and the US register study(32)is a valuable addition to the literature. Notably, although the majority of studies have sample sizes in the thousands(20,22,24,25,29–31), one even over 8,000,000(32) five studies in this review have relatively small sample sizes(19,21,26–28).

Limitations for this review as a whole, include the small number of studies which met the inclusion criteria and a high risk of publication bias across the included studies. Furthermore, our data extraction was performed by only one author. One question pinpointed at the beginning of this review, e.g. a specific gestational vulnerability timepoint, could not be fully elucidated based on the current body of evidence and the lack of replication multi-point measures across studies.

Discussion

This review of 13 studies supports the previous findings reviewed by Van den Bergh et al.(2017), suggesting that prenatal depression is associated with adverse neuropsychiatric consequences on the offspring. Ten studies(19,20,22,24–30) favored the conclusion that the

effects of maternal depression on offspring neuropsychiatric outcomes are specific to the maternal pregnancy period and are not accounted for by depression after pregnancy. Two studies(21,32), however, did not address the pre vs postnatal specificity question, and another(31) concluded that the offspring neuropsychiatric effects are not specific to the prenatal period, but are rather a consequence of maternal depression during the offspring postnatal development. As discussed previously, the one dissenting study used non-validated measures of maternal depression, which hampers its reliability(31). Importantly, maternal depression shows high continuity from pregnancy onwards, with study populations(20,30) indicating that in over 50% of the women, clinically relevant depressive symptomatology during pregnancy persists after delivery. Therefore, the question of exposure timing during pregnancy or after delivery of the maternal effects may be difficult to disentangle because of statistical multi-collinearity problems. Only the PREDO cohort from this review, with 14 by-weekly gestational measurements of maternal depressive symptoms was able to address the question of a specific vulnerability window, which showed that the effects on child problem behaviors were gestation week non-specific(20,30).

Pathways

Prenatal depressive symptoms may influence child neuropsychiatric outcomes via multiple psychological, health behavior, and biological pathways. An important component of understanding these pathways, involves disentangling the effects of other pregnancy and perinatal complications, which may contribute to the severity, duration, and complexity of maternal prenatal depression. For instance, recent meta-analyses and systematic reviews show that maternal obesity in early pregnancy is associated with an increased risk of depression during pregnancy(40,41). Also in the PREDO cohort, from a study not in this review, women with early

pregnancy overweight and obesity had consistently elevated depressive symptoms throughout pregnancy and after delivery(8). Evidence suggests that gestational diabetes and hypertension spectrum disorders may also be associated with prenatal depression(42), but these findings remain controversial(8).

Maternal cardio-metabolic conditions might contribute as one of the pathways, as a meta-analysis found that maternal obesity predicted an increased risk of autism and ADHD, developmental delay and emotional/behavioral problems in children(43). Also, we recently showed that maternal severe obesity in early pregnancy is associated with hyperactivity, sleep problems, conduct, externalizing and total problems, depressive symptoms, anxiety and ADHD problems in children(44). Gestational diabetes has repeatedly been associated with an increased risk of neuropsychiatric disorders, particularly of autism and schizophrenia in the offspring(45–48). Yet, in the PREDO maternal obesity or gestational diabetes were not associated with mother-rated internalizing, externalizing or total psychiatric problems in 1.9-5.9-year-old children (20), but were associated with child neurodevelopmental delay(49).

Prenatal depression also increases risks of preterm birth and low birth weight(42,50). Also in the PREDO cohort, maternal depressive symptoms during pregnancy predicted shorter gestation length(51). Preterm birth and low birth weight have been consistently shown to be risk factors for neuropsychiatric disorders(52–56), and in sibling comparisons(53,54).

Evidence from a meta-analysis and from large population-based studies suggests that depressed mothers are more likely to smoke throughout pregnancy(42,57), and prenatal smoking has been repeatedly associated with the risk of neuropsychiatric disorders in the offspring(20,58,59). Also in the PREDO, prenatal smoking was associated with increased internalizing, externalizing total psychiatric and ADHD problems in children(20,30).

Biological Mechanisms

The biological mechanisms possibly linking maternal depression and psychological distress more generally with offspring neuropsychiatric outcomes were reviewed in Van den Bergh et al.(2017)(2). According to this review, and studies published since, prenatal depression may be associated with child neurodevelopment via 1)alterations in hypothalamus-pituitary-adrenal(HPA)-axis functioning, 2) functional and structural changes of related brain areas including amygdala and prefrontal cortex, 3)changes in autonomic nervous system and 4) immune system functioning and in gut microbiota(2,60,61).

At population level, one of the most consistent biological changes in depression is altered cortisol levels, indicating altered HPA-axis functioning(2,62,63). However, studies linking maternal depression specifically during pregnancy with maternal or infant cortisol levels have yielded inconsistent findings(2,62,63). Yet, maternal HPA axis functioning during pregnancy has been linked with offspring neuropsychiatric problems(2). For instance, we recently showed that maternal licorice consumption during pregnancy predicted an over 3-fold risk of ADHD problems in the offspring(64) due to Glycyrrhizin, which inhibits the placental 11β -hydroxysteroid dehydrogenase type 2(*11\beta*HSD2) enzyme. This enzyme protects the fetus from maternal glucocorticoids, hence leaving the fetus vulnerable to maternal glucocorticoid excess. Furthermore, structural and functional changes in the infant amygdala, which regulates HPA axis functioning, have been repeatedly reported as a consequence of prenatal depression(2,65–67) and are also associated with child psychopathology risk(68,69). Also, alterations in the functioning of the autonomic nervous system that also plays a key role in the stress response have been found in children exposed to prenatal depression(2).

Changes in inflammatory pathways and gut microbiota, as a consequence of prenatal depression, offer another route through which prenatal depression may affect child neuropsychiatric problems. Maternal prenatal cytokine levels present questions for epigenetic programming as cytokines may pass through the placenta(70). Higher prenatal depression has also been directly associated with maternal inflammatory cytokine levels during pregnancy(71,72), but the findings are inconsistent. Correspondingly both anti-inflammatory drugs(73) and probiotics(74) have antidepressant effects. Prenatal levels of C-reactive protein(CRP), a key inflammatory marker, have been associated with offspring risk of different neuropsychiatric disorders (75–78), and prenatal depression is associated with offspring CRP levels(79). Evidence for the gut microbiota pathway predominately stems from animal studies but two recent studies have shown microbiota changes in offspring exposed to prenatal depression(80,81). Nonetheless, the biological mechanisms involved warrant further research.

Cellularly, depression-related changes in fetal biology studies have specifically focused on epigenetic modifications. There are several recent systematic reviews on the effects of maternal psychological distress during pregnancy and more specifically antenatal depression on placental and infant DNA methylation(2,82,83). Overall, these reviews state that the findings are inconsistent but many candidate gene studies have linked methylation of the *NR3C1*, the glucocorticoid-receptor gene, with maternal prenatal depression. Other potential, often examined, candidate genes include *11BHSD2*, *FKBP5*, *IGF2*, *SLC6A4*, *OXTR*, *CRH* and *BDNF*, genes that also play roles in HPA axis regulation. Most studies have focused on either assessing placental DNA methylation or infant cord-blood methylation levels. The studies have identified some significant effects, which still need validation. Future larger epigenome-wide-

association studies harmonizing and pooling data into meta-analyses will overcome the current single study limitations.

Recent findings from the PREDO suggest that changes in placental gene expression and infant DNA cord blood methylation as well as morphological changes in placental structure may be among the mediating biological pathways between antenatal depressive symptoms and child psychiatric problems. Among approximately 60 PREDO participants, prenatal depressive symptoms were associated with higher placental mRNA levels of glucocorticoid and mineralocorticoid receptor genes. Findings which suggest higher placental glucocorticoid sensitivity (84,85). In a UK longitudinal study among 93 participants, we found that higher prenatal depressive symptoms were associated with reduced placental IGF2-2 mRNA levels and, particularly in the placentas of female fetuses, with altered mRNA levels of several genes regulating fetal glucocorticoid exposure(86). Furthermore, among PREDO participants, maternal prenatal depressive symptoms were associated with lower infant epigenetic gestational age at birth, a biomarker of the developmental maturation level of the fetus. This biomarker predicted increased total and internalizing psychiatric problems in boys, and partially mediated the effects of maternal prenatal depression on boys' internalizing problems(87). Another PREDO study assessing placental morphology among 86 participants found less variation in placental villous barrier thickness of gamma-smooth muscle actin-negative villi in the placentas of antenatally depressed mothers, indicating reduced placental maturation, due to prenatal depression. This placental structural change predicted internalizing and total psychiatric problems in 60 toddlers(88).

Treatments of prenatal depression

Predictors for full recovery from prenatal depression include the absence of maternal health concerns, low total parental stress status, and limited child behavior issues(89), while maternal sensitivity has been found to attenuate the effects of maternal prenatal depression on toddler total problems (27), all which underscore the need for a comprehensive treatment approach for prenatal depression. Antidepressant medication may offer an option as several reviews indicate the likelihood of serious harms is low (12–15). Although, investigations into specific medications and classes of anti-depressants (90–92) complicate the literature, suggesting serious harmful effects, leading many doctors not to prescribe and/or many women refuse/discontinue medication in pregnancy(5). Until the data on the safety and efficacy of antidepressant therapies is clearly defined, efforts should be concentrated to assess alternative therapies. Although, they stray from antidepressants, pregnant women have reported an interest in cognitive behavioral therapy(5), which recent review evidence suggests has robust effects for the treatment of women with MDD(93). However, due to a lack of resources and limited access to standard therapies: nearly half of diagnosed women fail to receive timely evidence-based treatment(94). In lieu of standard delivery, online cognitive behavioral therapy interventions may serve as an effective measure for improving maternal perinatal mental health(95,96). Recent studies have considered the effectiveness of relaxation practices through musical therapy(97), fish oil supplementation (98), dietary supplementation(99) and future studies could consider probiotics supplements.

Conclusions

Our review found a limited amount of high to moderate quality evidence supporting the association of prenatal depression and neuropsychiatric outcomes in children, published 2014-2018. More, carefully conducted cohort studies with multi-time point, validated exposure and

outcome measures investigating epigenetic and protective factors are needed to further corroborate the findings relating to a specific developmental vulnerability period. Further investigations into the implications of the timing and consistency of exposure, confounding by other perinatal conditions, and possible biological mechanisms would bolster the evidence. Future research needs continuous and prospective measures of maternal depressive symptoms throughout pregnancy and beyond, in order to better scope the prenatal and postnatal trajectories of depression, risk factors, and include follow-up of offspring into adulthood to assess long-term neuropsychiatric effects.

Research Funding

Funding for this review comes from an Academy of Finland Program Grant, European Commission Horizon 2020 Award SC1-2016-RTD-733280 for RECAP, European Commission Dynamics of Inequality Across the Life-course: structures and processes(DIAL) No 724363 for PremLife, and the Signe and Ane Gyllenberg Foundation.

Disclosure

The authors declare no conflict of interest.

References

1. O'Donnell KJ, Meaney MJ. Fetal Origins of Mental Health: The Developmental Origins of Health and Disease Hypothesis. *Am J Psychiatry* [Internet] 2017 [cited 2018 Apr 26];174:319–28.
2. Van den Bergh BRH, van den Heuvel MI, Lahti M, et al. Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. *Neurosci Biobehav Rev* [Internet] 2017;
3. Gluckman PD, Hanson MA. The developmental origins of health and disease: an overview. *Dev Orig Heal Dis* 2006;1–5.
4. Barker DJP. The origins of the developmental origins theory. *J Intern Med* [Internet] 2007 [cited 2018 May 3];261:412–7.
5. Goodman JH. Women's Attitudes, Preferences, and Perceived Barriers to Treatment for Perinatal Depression. *Birth* [Internet] 2009 [cited 2018 Apr 26];36:60–9.
6. Bauer A, Parsonage M, Knapp M, Iemmi V, Adelaja B. Centre For Mental Health | Costs of perinatal mental health problems [Internet]. [cited 2018 May 7];
7. Sally Russell, Dr Beckie Lang, Jacqui Clinton, Dr Cheryll Adams JL. *Mental Health Experiences of Women and Health*. 2013.
8. Kumpulainen SM, Girchenko P, Lahti-Pulkkinen M, et al. Maternal early pregnancy obesity and depressive symptoms during and after pregnancy. *Psychol. Med.* 2018;1–11.
9. Girchenko P, Lahti M, Tuovinen S, et al. Cohort Profile: Prediction and prevention of preeclampsia and intrauterine growth restriction (PREDO) study. *Int J Epidemiol*

Review: Depression & Offspring

- 2017;46:1380–1381g.
10. Jarde A, Morais M, Kingston D, et al. Neonatal outcomes in women with untreated antenatal depression compared with women without depression: A systematic review and meta-analysis. *JAMA Psychiatry* 2016;73:826–37.
 11. Gentile S. Untreated depression during pregnancy: Short- and long-term effects in offspring. A systematic review. *Neuroscience [Internet]* 2017;342:154–66.
 12. Andalib S, Emamhadi MR, Yousefzadeh-Chabok S, et al. Maternal SSRI exposure increases the risk of autistic offspring: A meta-analysis and systematic review. *Eur Psychiatry [Internet]* 2017;45:161–6.
 13. Gentile S, Fusco ML. Placental and fetal effects of antenatal exposure to antidepressants or untreated maternal depression. *J Matern Fetal Neonatal Med [Internet]* 2017;30:1189–99.
 14. Ornoy A, Weinstein-Fudim L, Ergaz Z. Antidepressants, Antipsychotics, and Mood Stabilizers in Pregnancy: What Do We Know and How Should We Treat Pregnant Women with Depression. *Birth Defects Res [Internet]* 2017;109:933–56.
 15. Mezzacappa A, Lasica PA, Gianfagna F, et al. Risk for Autism Spectrum Disorders According to Period of Prenatal Antidepressant Exposure A Systematic Review and Meta-analysis. *JAMA Pediatr [Internet]* 2017;171:555–63.
 16. Moher D, Liberati A, Tetzlaff J AD. PRISMA 2009 Flow Diagram. *Prism. statement.* 2009;6:1000097.
 17. Wells GA, Shea B, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing

- the quality of nonrandomized studies in meta-analyses. *Ottawa Hosp Res Inst* [Internet] 2013;1–4.
18. Higgins J, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* [Internet]. Version 5. The Cochrane Collaboration; 2011.
 19. Korhonen M, Luoma I, Salmelin R, Tamminen T. Maternal depressive symptoms: associations with adolescents' internalizing and externalizing problems and social competence. *Nord J Psychiatry* 2014;68:323–32.
 20. Lahti M, Savolainen K, Tuovinen S, et al. Maternal Depressive Symptoms During and After Pregnancy and Psychiatric Problems in Children. *J Am Acad Child Adolesc Psychiatry* [Internet] 2017;56:30–39.e7.
 21. Eichler A, Walz L, Grunitz J, et al. Children of Prenatally Depressed Mothers: Externalizing and Internalizing Symptoms are Accompanied by Reductions in Specific Social-Emotional Competencies. *J Child Fam Stud* 2017;26:3135–44.
 22. El Marroun H, White TJH, van der Knaap NJF, et al. Prenatal exposure to selective serotonin reuptake inhibitors and social responsiveness symptoms of autism: population-based study of young children. *Br J Psychiatry* 2014;205:95–102.
 23. Hermansen TK, Røysamb E, Augusti E-M, Melinder A. Behavior and inhibitory control in children with prenatal exposure to antidepressants and medically untreated depression. 2016 [cited 2018 Jun 18];
 24. Leis JA, Heron J, Stuart EA, Mendelson T. Associations Between Maternal Mental Health and Child Emotional and Behavioral Problems: Does Prenatal Mental Health Matter?

- 2013 [cited 2018 Jun 26];
25. O'Donnell KJ, Glover V, Barker ED, O'Connor TG. The persisting effect of maternal mood in pregnancy on childhood psychopathology. *Dev Psychopathol* 2014;
 26. Plant DT, Pariante CM, Sharp D, Pawlby S. Prenatal depression and offspring depression in adulthood: role of child maltreatment. *Br J Psychiatry* [Internet] 2015 [cited 2018 Jun 26];207:213–20.
 27. Edwards RC, Hans SL. Prenatal Depressive Symptoms and Toddler Behavior Problems: The Role of Maternal Sensitivity and Child Sex. *Child Psychiatry Hum Dev* 2016;47:696–707.
 28. Johnson KC, Smith AK, Stowe ZN, Newport DJ, Brennan PA. Preschool Outcomes Following Prenatal Serotonin Reuptake Inhibitor Exposure: Differences in Language and Behavior, but Not Cognitive Function. *J Clin Psychiatry* 2016;77:E176–82.
 29. Capron LE, Glover V, Pearson RM, et al. Associations of maternal and paternal antenatal mood with offspring anxiety disorder at age 18 years. *J Affect Disord* [Internet] 2015 [cited 2018 Jun 26];187:20–6.
 30. Wolford E, Lahti M, Tuovinen S, et al. Maternal depressive symptoms during and after pregnancy are associated with attention-deficit/hyperactivity disorder symptoms in their 3- to 6-year-old children. *PLoS One* 2017;12.
 31. Gjerde LC, Eilertsen EM, Reichborn-Kjennerud T, et al. Maternal perinatal and concurrent depressive symptoms and child behavior problems: a sibling comparison study. *J Child Psychol Psychiatry* 2017;58:779–86.

32. Wieckowski BM, Mukhtar Y, Lee JJ, Xing G, Walker CK. Higher autism in children of women with psychiatric diagnoses. *Res Autism Spectr Disord* 2017;33:10–20.
33. Su K-P, Chiu T-H, Huang C-L, et al. Different cutoff points for different trimesters? The use of Edinburgh Postnatal Depression Scale and Beck Depression Inventory to screen for depression in pregnant Taiwanese women. *Gen Hosp Psychiatry* [Internet] 2007 [cited 2018 Jun 27];29:436–41.
34. Harris B, Huckle P, Thomas R, Johns S, Fung H. The use of rating scales to identify post-natal depression. *Br J Psychiatry* [Internet] 1989 [cited 2018 Jun 27];154:813–7.
35. Tambs K, Røysamb E. Selection of questions to short-form versions of original psychometric instruments in MoBa. *Nor Epidemiol* [Internet] 2014 [cited 2018 Jun 20];24:195–201.
36. Gjerde LC, Røysamb E, Czajkowski N, et al. Strong Genetic Correlation Between Interview-Assessed Internalizing Disorders and a Brief Self-Report Symptom Scale. *Twin Res Hum Genet* [Internet] 2011 [cited 2018 May 2];14:64–72.
37. McBride O, Bebbington P, Cooper C. Could the lower prevalence of affective disorder in older people be due to measurement error? Reliability of the Revised Clinical Interview Schedule in younger and older adults. *J Affect Disord* [Internet] 2013 [cited 2018 Jun 27];148:310–5.
38. Briggs-Gowan MJ, Carter AS, Irwin JR, Wachtel K, Cicchetti D V. The Brief Infant-Toddler Social and Emotional Assessment: Screening for Social-Emotional Problems and Delays in Competence. [cited 2018 Jul 30];

39. Coll CVN, Domingues MR, Goncalves H, Bertoldi AD. Perceived barriers to leisure-time physical activity during pregnancy: A literature review of quantitative and qualitative evidence. *J Sci Med Sport* [Internet] 2017;20:17–25.
40. Molyneaux E, Poston L, Ashurst-williams S, Howard LM. Obesity and mental disorders during pregnancy and postpartum: a systematic review and meta-analysis. *Obstet Gynecol* 2014;123:857–67.
41. Steinig J, Nagl M, Linde K, Zietlow G, Kersting A. Antenatal and postnatal depression in women with obesity: a systematic review. *Arch Womens Ment Heal* [Internet] 2017;20:569–85.
42. Räisänen S, Lehto SM, Nielsen HS, Gissler M, Kramer MR, Heinonen S. Risk factors for and perinatal outcomes of major depression during pregnancy: A population-based analysis during 2002-2010 in Finland. *BMJ Open* 2014;4.
43. Sanchez CE, Barry C, Sabhlok A, et al. Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: A meta-analysis. *Obes Rev* 2017;
44. Mina TH, Lahti M, Drake AJ, et al. Prenatal exposure to very severe maternal obesity is associated with adverse neuropsychiatric outcomes in children. *Psychol Med* 2017;47:353–62.
45. Nahum Sacks K, Friger M, Shoham-Vardi I, et al. Prenatal exposure to gestational diabetes mellitus as an independent risk factor for long-term neuropsychiatric morbidity of the offspring. *Am J Obstet Gynecol* [Internet] 2016;215:380.e1-380.e7.
46. Wan H, Zhang C, Li H, Luan S, Liu C. Association of maternal diabetes with autism

- spectrum disorders in offspring: A systemic review and meta-analysis. *Medicine* (Baltimore) [Internet] 2018;97:e9438.
47. Van Lieshout RJ, Voruganti LP. Diabetes mellitus during pregnancy and increased risk of schizophrenia in offspring: A review of the evidence and putative mechanisms. *J Psychiatry Neurosci* 2008;33:395–404.
 48. Xiang AH, Wang X, Martinez MP, et al. Association of maternal diabetes with autism in offspring. *JAMA - J Am Med Assoc* 2015;313:1425–34.
 49. Girchenko P, Tuovinen S, Lahti-Pulkkinen M, et al. Maternal early pregnancy obesity and related pregnancy and pre-pregnancy disorders: associations with child developmental milestones in the prospective PREDO Study. *Int J Obes* [Internet] 2018 [cited 2018 May 7];
 50. Jarde A, Morais M, Kingston D, et al. Neonatal outcomes in women with untreated antenatal depression compared with women without depression: A systematic review and meta-analysis. *JAMA Psychiatry* 2016;73:826–37.
 51. Pesonen AK, Lahti M, Kuusinen T, et al. Maternal prenatal positive affect, depressive and anxiety symptoms and birth outcomes: The PREDO study. *PLoS One* [Internet] 2016;11:1–13.
 52. Pyhälä R, Wolford E, Kautiainen H, et al. Self-Reported Mental Health Problems Among Adults Born Preterm: A Meta-Analysis. *Pediatrics* [Internet] 2017;139:e20162690.
 53. D’Onofrio BM, Class QA, Rickert ME, Larsson H, Långström N, Lichtenstein P. Preterm birth and mortality and morbidity: a population-based quasi-experimental study. *JAMA*

- psychiatry [Internet] 2013 [cited 2016 Oct 8];70:1231–40.
54. Class QA, Rickert ME, Larsson H, Lichtenstein P, D’Onofrio BM. Fetal growth and psychiatric and socioeconomic problems: population-based sibling comparison. *Br J Psychiatry* [Internet] 2014 [cited 2016 Oct 8];205:355–61.
 55. Räikkönen K, Pesonen A-K, Heinonen K, et al. Depression in young adults with very low birth weight: the Helsinki study of very low-birth-weight adults. *Arch Gen Psychiatry* 2008;65:290–6.
 56. Heinonen K, Kajantie E, Pesonen A-K, et al. Common mental disorders in young adults born late-preterm. *Psychol Med* [Internet] 2016;46:2227–38.
 57. Riaz M, Lewis S, Naughton F, Ussher M. Predictors of smoking cessation during pregnancy: A systematic review and meta-analysis. *Addiction* 2018;610–22.
 58. Ekblad M, Lehtonen L, Korkeila J, Gissler M. Maternal Smoking During Pregnancy and the Risk of Psychiatric Morbidity in Singleton Sibling Pairs. *Nicotine Tob Res* [Internet] 2017;19:597–604.
 59. Quinn PD, Rickert ME, Weibull CE, et al. Association Between Maternal Smoking During Pregnancy and Severe Mental Illness in Offspring. *JAMA Psychiatry* [Internet] 2017;74:589.
 60. Stetler C, Miller GE. Depression and Hypothalamic-Pituitary-Adrenal Activation: A Quantitative Summary of Four Decades of Research. *Psychosom Med* [Internet] 2011 [cited 2018 Apr 26];73:114–26.
 61. Zorn J V., Schür RR, Boks MP, Kahn RS, Joëls M, Vinkers CH. Cortisol stress reactivity

- across psychiatric disorders: A systematic review and meta-analysis.
- Psychoneuroendocrinology [Internet] 2017 [cited 2018 Apr 26];77:25–36.
62. Bleker LS, Roseboom TJ, Vrijkotte TG, Reynolds RM, de Rooij SR. Determinants of cortisol during pregnancy - The ABCD cohort. Psychoneuroendocrinology [Internet] 2017;83:172–81.
 63. Thomas JC, Letourneau N, Bryce CI, Campbell TS, Giesbrecht GF. Biological embedding of perinatal social relationships in infant stress reactivity. Dev Psychobiol [Internet] 2017;59:425–35.
 64. Räikkönen K, Martikainen S, Pesonen A-K, et al. Maternal Licorice Consumption During Pregnancy and Pubertal, Cognitive, and Psychiatric Outcomes in Children. Am J Epidemiol [Internet] 2017 [cited 2018 May 11];185:317–28.
 65. van der Knaap NJF, Klumpers F, El Marroun H, et al. Maternal depressive symptoms during pregnancy are associated with amygdala hyperresponsivity in children. Eur Child Adolesc Psychiatry [Internet] 2017;3–10.
 66. Soe NN, Wen DJ, Poh JS, et al. Perinatal maternal depressive symptoms alter amygdala functional connectivity in girls. Hum Brain Mapp 2018;39:680–90.
 67. Wen DJ, Poh JS, Ni SN, et al. Influences of prenatal and postnatal maternal depression on amygdala volume and microstructure in young children. Transl Psychiatry [Internet] 2017;7:e1103.
 68. Buss C, Davis EP, Shahbaba B, Pruessner JC, Head K, Sandman CA. Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes

- and affective problems. *Proc Natl Acad Sci U S A* [Internet] 2012 [cited 2018 Apr 26];109:E1312-9.
69. Rogers CE, Sylvester CM, Mintz C, et al. Neonatal Amygdala Functional Connectivity at Rest in Healthy and Preterm Infants and Early Internalizing Symptoms. *J Am Acad Child Adolesc Psychiatry* [Internet] 2017 [cited 2018 Apr 26];56:157–66.
70. Zaretsky M V., Alexander JM, Byrd W, Bawdon RE. Transfer of inflammatory cytokines across the placenta. *Obstet Gynecol* 2004;103:546–50.
71. Shelton MM, Schminkey DL, Groer MW. Relationships among prenatal depression, plasma cortisol, and inflammatory cytokines. *Biol Res Nurs* [Internet] 2015 [cited 2018 Apr 26];17:295–302.
72. Karlsson L, Nousiainen N, Scheinin NM, et al. Cytokine profile and maternal depression and anxiety symptoms in mid-pregnancy-the FinnBrain Birth Cohort Study. *Arch Womens Ment Heal* [Internet] 2017;20:39–48.
73. Köhler O, Benros ME, Nordentoft M, et al. Effect of Anti-inflammatory Treatment on Depression, Depressive Symptoms, and Adverse Effects. *JAMA Psychiatry* [Internet] 2014 [cited 2018 Apr 26];71:1381.
74. Huang R, Wang K, Hu J. Effect of Probiotics on Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients* [Internet] 2016 [cited 2018 Apr 26];8:483.
75. Canetta S, Sourander A, Surcel H-M, et al. Elevated Maternal C-Reactive Protein and Increased Risk of Schizophrenia in a National Birth Cohort. *Am J Psychiatry* [Internet]

- 2014 [cited 2018 Apr 26];171:960–8.
76. Brown AS, Sourander A, Hinkka-Yli-Salomäki S, McKeague IW, Sundvall J, Surcel H-M. Elevated maternal C-reactive protein and autism in a national birth cohort. *Mol Psychiatry* [Internet] 2014 [cited 2018 Apr 26];19:259–64.
77. Zerbo O, Traglia M, Yoshida C, et al. Maternal mid-pregnancy C-reactive protein and risk of autism spectrum disorders: the early markers for autism study. *Transl Psychiatry* [Internet] 2016 [cited 2018 Apr 26];6:e783.
78. Gilman SE, Cherkerzian S, Buka SL, Hahn J, Hornig M, Goldstein JM. Prenatal immune programming of the sex-dependent risk for major depression. *Transl Psychiatry* [Internet] 2016 [cited 2018 Apr 26];6:e822–e822.
79. Plant DT, Pawlby S, Sharp D, Zunszain PA, Pariante CM. Prenatal maternal depression is associated with offspring inflammation at 25 years: a prospective longitudinal cohort study. *Transl Psychiatry* [Internet] 2016 [cited 2018 Apr 26];6:e936.
80. Kang LJ, Koleva PT, Field CJ, et al. Maternal depressive symptoms linked to reduced fecal Immunoglobulin A concentrations in infants. *Brain Behav Immun* [Internet] 2018;68:123–31.
81. Krause L, Einsle F, Petzoldt J, Wittchen HU, Martini J. The role of maternal anxiety and depressive disorders prior to and during pregnancy and perinatal psychopathological symptoms for early infant diseases and drug administration. *Early Hum Dev* [Internet] 2017;109:7–14.
82. Ryan J, Mansell T, Fransquet P, Saffery R. Does maternal mental well-being in pregnancy

- impact the early human epigenome? *Epigenomics* 2017;9:313–32.
83. Palma-Gudiel H, Córdova-Palomera A, Eixarch E, Deuschle M, Fañanás L. Maternal psychosocial stress during pregnancy alters the epigenetic signature of the glucocorticoid receptor gene promoter in their offspring: A meta-analysis. *Epigenetics* 2015;10:893–902.
84. Räikkönen K, Pesonen AK, O'Reilly JR, et al. Maternal depressive symptoms during pregnancy, placental expression of genes regulating glucocorticoid and serotonin function and infant regulatory behaviors. *Psychol Med* 2015;45:3217–26.
85. Reynolds RM, Pesonen A-K, O'Reilly JR, et al. Maternal depressive symptoms throughout pregnancy are associated with increased placental glucocorticoid sensitivity. *Psychol Med* 2015;45.
86. Mina TH, Räikkönen K, Riley SC, Norman JE, Reynolds RM. Maternal distress associates with placental genes regulating fetal glucocorticoid exposure and IGF2: Role of obesity and sex. *Psychoneuroendocrinology* 2015;59:112–22.
87. Suarez A, Lahti J, Czamara D, et al. The Epigenetic Clock at Birth: Associations With Maternal Antenatal Depression and Child Psychiatric Problems. *J Am Acad Child Adolesc Psychiatry* [Internet] 2018;
88. Lahti-Pulkkinen M, Cudmore MJ, Haeussner E, et al. Placental Morphology Is Associated with Maternal Depressive Symptoms during Pregnancy and Toddler Psychiatric Problems. *Sci Rep* [Internet] 2018;8:791.
89. Shankar R, Badker R, Brain U, Oberlander TF, Misri S. Predictors of Recovery from Depression and Anxiety in Women: A Longitudinal Study from Childbirth to 6 Years.

- Can J Psychiatry-Revue Can Psychiatr 2017;62:318–26.
90. Kong LL, Zhou TT, Wang BL, Gao ZB, Wang CX. The risks associated with the use of lamotrigine during pregnancy. *Int J Psychiatry Clin Pract* [Internet] 2018;22:2–5.
 91. Paulzen M, Goecke TW, Stingl JC, et al. Pregnancy exposure to citalopram - Therapeutic drug monitoring in maternal blood, amniotic fluid and cord blood. *Prog Neuropsychopharmacol Biol Psychiatry* [Internet] 2017;79:213–9.
 92. Siu AL, Bibbins-Domingo K, Grossman DC, et al. Screening for Depression in Adults. *JAMA* [Internet] 2016 [cited 2018 Apr 26];315:380.
 93. van Ravesteyn LM, Lambregtse-van den Berg MP, Hoogendijk WJG, Kamperman AM. Interventions to treat mental disorders during pregnancy: A systematic review and multiple treatment meta-analysis. *PLoS One* 2017;12.
 94. Marian Knight, Manisha Nair, Derek Tuffnell JS, Sara Kenyon JJK (Eds. . Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2013–15 [Internet]. 2017.
 95. Ashford MT, Ayers S, Olander EK. Supporting women with postpartum anxiety: exploring views and experiences of specialist community public health nurses in the UK. *Health Soc Care Community* [Internet] 2017;25:1257–64.
 96. Lee EW, Denison FC, Hor K, Reynolds RM. Web-based interventions for prevention and treatment of perinatal mood disorders: a systematic review. *BMC Pregnancy Childbirth* [Internet] 2016 [cited 2018 Apr 26];16:38.
 97. Nwebube C, Glover V, Stewart L. Prenatal listening to songs composed for pregnancy and

- symptoms of anxiety and depression: a pilot study. *BMC Complement Altern Med* [Internet] 2017;17:256.
98. Farshbaf-Khalili A, Mohammad-Alizadeh S, Farshbaf-Khalili A, Mohammadi F, Ostadrahimi A. Fish-Oil Supplementation and Maternal Mental Health: A Triple-Blind, Randomized Controlled Trial. *Iran Red Crescent Med J* [Internet] 2017;19.
99. Sparling TM, Henschke N, Nesbitt RC, Gabrysch S. The role of diet and nutritional supplementation in perinatal depression: a systematic review. *Matern Child Nutr* 2017;13.

Figure 1. PRISMA Flow Diagram: Study inclusion and exclusion process

Author accepted manuscript

Review: Depression & Offspring

Table Summary of Included Study Characteristics & Main

Stud	Sourc	Populati	Sampl Siz	Study	Maternal Measureme	Offspring Measureme	Result
							Statistical
FINLAND							
Korhonen et al. 2014	Finnish longitudinal cohort study	Finnish mother- child dyads	192	cohort	Prenatal: EPDS ⁴ in the last trimester Postnatal: EPDS ⁴ 2 weeks, 2 months, 6 months, 4-5 years, 8-9 years & 16-17 years	CBCL ¹ & YSR ¹¹ at multiple times up to age 16	Time of the initial exposure for maternal adolescent CBCL/YSR outcomes were significant Initial Prenatal (Last trimester) exposure Initial Postnatal (2 months) exposure & 16-17 years standard effect size 0.90 (YSR) Initial Postnatal externalizing problems: P=0.003, standard effect size Adjusted Covariates: Int.Epis.Time
Lahti et al 2017	PREDO ¹	Finnish, mother- child dyads	2296	cohort	Prenatal: CES-D Bi- weekly between weeks+days 12+0/13+6 and 38+0/39+6 or delivery. Postnatal: Becks Depression Inventory 1½–5 years	CBCL ⁶ at ages 1.9- 5.9years	Maternal depressive symptoms during pregnancy predicted significantly higher internalizing (0.28 SD unit per SD unit in [95% CI = 0.24, 0.32]), externalizing (0.28 SD unit 0.30]), and total problems (0.31 [0.27, 0.35]) in children. Adjusted Covariates: Hist.Dep, Antidep., PPH, M.Diab., Sex, GL, BWT, Fam.Stat., ADP, M.Edu, CA
Wolford et al 2017	PREDO	Finnish, mother- child dyads	1779	cohort	Prenatal: CES-D Bi- weekly between weeks+days 12+0/13+6 and 38+0/39+6 or delivery. Postnatal: Becks Depression Inventory 1½–5 years	CHI questions (ADHD) at 3-6 years old	Children of mothers with consistently high levels of showed higher average levels (MD = 0.46 SD units, 95% CI 0.36, 0.56, p < 0.001 group), and proportion (32.1% vs. 14.7%) and odds ratio (OR = p < 0.001) of clinically significant ADHD symptoms Adjusted Covariates: M.ADHD, Hist.Dep, Antidep., PPH, M.Diab., Sex, GL, BWT, Fam.Stat., ADP,, M.Edu, CA
NORWAY							
Gjerde 2017	MoBA	11,599 Norwegian families	17830 siblings	cohort	Prenatal: SCL-90 Short form SCL-5 and SCL-8 selfrating questionnaires 17th week & 30th week gestation Postnatal: 6 months, 18 months, 3 years & 5 years after birth	CBCL ⁶ at 1.5, 3 and 5-years	In sibling comparison, concurrent maternal depression was significantly associated with internalizing [estimate = 2.82(1.91, 3.73, 95% CI)] and externalizing problems [estimate = 2.40(1.56, 3.23, 95% CI)] Adjusted Covariates: M. CA, Sex, Par., M.Edu
GERMANY							
Eichler et al 2017	FRANCES	German, mother- child dyads randomly selected from the FRAMES study population	204	case-control	Prenatal: EPDS 3rd trimester Postnatal: EPDS 6-9 years	Parental Questionnaire from ICD-10 and DSM-IV aged 6-9	Total Sample: 6.74(4.95) , Mother not depressed: Mother depressed: 13.07(3.01) Not-depressed vs. depressed: -21.7** P < 0.001 Adjusted Covariates: Sex, Fam.Stat., CMD
THE NETHERLANDS							

Review: Depression & Offspring

El Marroun et al. 2014	Dutch mothers-child dyads & father-child dyads	5976	Cohort	Prenatal SSRI Exposure: 1) SSRI use self-report, 2) pharmacy prescription records	CBCL & SRS ¹³ at ages 1.5, 3 and 6 years	Maternal depressive symptoms (without rated child affective problems (OR=1.44). Maternal depressive symptoms (without child affective problems were also significant (OR=2.45, P=0.03) Prenatal depressive symptoms as a control associated with affective problems (OR=1.44, P=0.001). Maternal prenatal depressive symptoms had more pervasive developmental problems (OR=1.93, 95% CI 1.53, 2.66). Maternal prenatal depressive symptoms after adjusting for depression at age 3 had more pervasive developmental problems (OR=1.93, p=0.02) Maternal prenatal depressive symptoms associated with autistic traits (β=0.05, 95% CI 0.01, 0.08, P=0.001)
UNITED KINGDOM						
Capron 2014 ALSPAC ¹⁴	Avon region, UK Mother-Father-Child triads	4303	Cohort	Prenatal: EPDS ⁴ at 18 weeks gestation Postnatal: EPDS ⁴ 8 weeks & 21 months	CIS-R ¹⁶ at age 18 years	Maternal prenatal depressive symptoms associated with autistic traits (β=0.05, 95% CI 0.03, 0.07) Direct comparison of the effect estimate for symptoms without SSRI use (β=0.09, 95% CI 0.03, 0.15, P=0.001) Adjusted Covariates: MA, Sex, M.Edu, ethnic
Leis et al 2014	ALSPAC ¹⁴ Avon region, UK Mother-Teacher-Child triads	2891	Cohort	Prenatal: EPDS ⁴ at 18 & 32 weeks gestation Postnatal: EPDS ⁴ at 8 weeks, 8, 21, 33, 61 & 73 months	SDQ ¹⁷ at age 10-11 years	Children exposed to elevated levels of maternal depression (>13 EPDS) at one time-point had higher SDQ scores (adjusted β (SE)) for: (hyperactivity) 0.35(0.13) p <0.01 (also significant for teacher rated SDQ) (emotional symptoms) 0.24 (0.09) p <0.01 (conduct problems) 0.20 (0.08) p <0.01 (also significant for teacher rated SDQ) (peer problems) 0.10 (0.05) p <0.05 (total problems) 1.00 (0.27) p <0.001 (also significant for teacher rated SDQ) Adjusted Covariates: MA, BWT, Sex, SDP, ADP, M.Edu, Fam.Stat.
O'Donnell et al. 2014	ALSPAC Avon region, UK Mother-Child dyads	7944	Cohort	Prenatal: EPDS ⁴ 18 weeks gestation Postnatal: EPDS at 8 weeks & 33 months postpartum	SDQ ¹⁷ at age 4, 7, 9, 11.5 & 13 years	<u>Intercept</u> Maternal prenatal depression (32 weeks) 0.077 Maternal postnatal depression (8 weeks) 0.127 Maternal depression at 33 months post. 0.183 Adjusted Covariates: MA, M.Edu, SEI, BWT, GA, Sex, SDP, ADP, P

Review: Depression & Offspring

Plant et al. 2015	SLCDS ¹⁷	UK mother-child dyads	103	Cohort	Prenatal: CIS-R ¹⁶ at 20 & 36 weeks gestation Postnatal: CIS-R ¹⁶ at 3 months & 12 months SADS-L ¹⁸ at 4 years, 11, and 16 years	Structured Clinical Interview for DSM-IV Axis I Disorders at age 25	Offspring exposed to maternal prenatal depression in adulthood. OR=3.4(95% CI 1.15, 8.1) $X^2(1)=8.4$, $p=0.002$ Mean number of depressive symptoms in offspring exposed to prenatal depression ($M=3.4$, $SD=2.1$) was significantly higher than those unexposed ($M=1.7$, $SD=2.1$, $z=3.4$, $p<0.001$) Maternal depression in the postnatal period was associated with adult depression: OR=1.8, (95% CI 0.8, 4.2) $X^2(1)=2.1$, $p=0.15$ Maternal depression in offspring childhood was associated with depression in adulthood OR=4.2 (95% CI 1.8, 10.2) $X^2(1)=11.1$, $p=0.001$ Maternal prenatal depression effects on offspring adult depression were partially mediated by childhood maltreatment $B=0.002$ (95% CI -0.001, 0.004) Adjusted Covariates: MA, ethnicity, SES, Maltreatment, SDP, ADP, GA, BWT, Sex, Ethnicity, C.Edu, C.IQ
UNITED STATES OF AMERICA							
Edwards et al. 2016	US longitudinal study	Young, low SES, African American mother-child dyads	196	Cohort	Prenatal: CES-D during pregnancy Postnatal: CES-D at 24 months	BITSEA at age 24 months	Path analysis Prenatal Depression → maternal Sensitivity (Full Sample) B(SE) 0.031 (0.02) (Boys) B (SE) 0.052 (0.035) 95% (Girls) B (SE) 0.002 (0.015) 95% Prenatal Depression → 24 month depression (Full Sample) B(SE) 0.086 (0.03) (Boys) B (SE) 0.073 (0.016) 95% (Girls) B (SE) 0.097 (0.061) 95% 0.016, 0.225) Adjusted Covariates: Sex, maternal education, maternal depression
Johnson 2016	Emory Women's	Clinical sample of USA Mother-child-child triads	178	Clinical, observational	Prenatal: BDI ⁷ during pregnancy Postnatal: BDI at follow-up	CBCL ⁶ PDD ¹⁵ in sibling pairs at ages 2.5-5 years	Children exposed to prenatal depression scored higher than unexposed children to score in the high risk range on the PDD

- Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction Adjusted Covariates: Antidep. (Antidepressant Use), ACDP (Alcohol Consumption During Pregnancy),
- Center for Epidemiologic Studies Depression Scale Apgar(Apgar Score),BWT (Birthweight), CA(Child Age), C.EarlyLearn.(Child Early Learning Center
- Franconian Cognition and Emotion Studies(Follow-up study to the FRAMES cohort)
- Edinburgh Postnatal Depression Scale attendance), C.Ethnicity (Child ethnicity), C.IQ (Child IQ score) C. Mal.(childhood maltreatment),
- Norwegian Mother and Child Cohort study CMD(Concurrent Maternal Depression), Deliv.Meth.(Delivery Method), Deliv.Comp(Delivery Complications),
- Child Behavior Checklist
- Beck Depression Inventory/ Beck Depression Inventory II Fam.Stat (Family Status), GA(Gestational Age), GL(gestational length), GDH(Gestational
- Selective Serotonin Reuptake Inhibitors Diabetes/Hypertension), Glob.Funct.(Global assessment of Functioning), HC(Head Circumference),
- Medically untreated depression group Hist.Dep(History of Diagnosed Depression) , Int.Epis.Time (Initial episode timing), M.ADHD (Maternal ADHD),
- Control group
- Youth Self Reports MA (Maternal Age), MDep(Maternal Prenatal Depressive Symptoms), M.Edu(Maternal Education Status), M.

Review: Depressive & Offspring
Health
Program

(mother rated): $\beta = -0.163$ Unstandardized
0.001, 0.002, $P=0.048$)*
Adjusted Covariates: CA, Sex, MA, Fam.S
SDP, ADP, Antidep., Psycho.Meds, BWT,
DelivComp, NumbComp, MDep, MoodEpi

Wieckowski et al 2017	Hospital discharge records	California singleton births occurring 1/1/91- 8951763 12/31/08	retrospective cohort	Medical records ICD-9- CM code for Depressive disorder NOS 311.x Anytime in the prenatal or perinatal period	California Dept. Of Developmental services diagnosis (Autism) age 4- 21years	Mothers diagnosed with one individual psychiatric condition were 1.2-2.8 times more likely to have a child who developed autism. Mothers diagnosed with any other more psychiatric condition were twice as likely to have a child with autism compared with unaffected or unreported women 1.97; 95% CI 1.83, 2.12). Adjusted Covariates: M.Origin, MA, M.Edu, Ethnicity
12.	Brief Symptom Inventory	Ethnicity (Maternal Ethnicity), M.Occup (Maternal Occupation/Status), M.Epilep.Stat.(Maternal Epileptic Status),				
13.	Social Response Scale	MoodEpi.(Mood Episodes), Numb.Comp(Number of Pregnancy Complications), Par. (Parity),				
14.	Avon Longitudinal Study of Parents and Children					
15.	Pervasive Developmental Disorders (CBCL Subscale)	Pater.Anxi.(Paternal pre/postnatal Anxiety), Parent.Index(Parenting Index Score), PE(Pre-Eclampsia, Mom16. Clinical Interview Schedule- Revised dad(mother-father relationship), PD(paternal depression), PND(Postnatal depression), PNDA(Maternal Postnatal				
17.	South London Child Development Study	Depression & Anxiety), PPObes.(Pre-Pregnancy Obesity),				
18.	Schedule for Affective Disorders and Schizophrenia	Psycho.Vari.(Psychological Variables), SDP(Smoking During Pregnancy)				

Table 2. NOS Quality of Evidence (Table listed in order of source country and then alphabetically.)

The Newcastle-Ottawa Scale assesses studies on 3 domains: Selection of study participants, Comparability of the studies, and the selection of the Outcomes. A study can receive a maximum of 4 stars in the Selection domain, 2 stars in the comparability domain, and 3 stars in the Outcomes domain.

Quality Assessment Criteria	Selection (****)					Comparability (**)		Outcome	
	Representativeness of exposed cohort?	Selection of the non-exposed cohort?	Ascertainment of exposure?	Demonstration that outcome of interest was not present at start of study?			Study controls for sex?	Study controls for at least one additional factor?	Assessment of outcome?
Acceptable (*)	Representative of average in community	Drawn from same community as exposed cohort	Secured records, Structured interview	Children born, outcome possible.	not therefore not yet	Yes	Age, pre-pregnancy obesity, gestational length, current maternal depression status, gestational diabetes/hypertension, pre-eclampsia, smoking & alcohol use during pregnancy, mother-father relationship, paternal depression, childhood maltreatment	Independent blind assessment, record linkage	Follow-up period sufficient measure outcome
Korhonen et al. 2014	★	★		★			★		★
Lahti et al. 2017	★	★		★		★	★		★
Wolford et al. 2017	★	★		★		★	★		★
Gjerde et al. 2017	★	★		★		★	★		★

Review: Depression & Offspring

Eichler et al. 2017	★	★		★	★	★		★
El Marroun et al. 2014	★	★		★	★	★	★	★
Capron et al. 2014	★	★		★		★		★
Leis et al. 2014	★	★		★	★	★		★
O'Donnell et al. 2014	★	★		★	★	★		★
	★	★		★	★	★		★
Plant et al. 2015	★	★	★	★	★	★	★	★
Edwards et al. 2016	★	★		★	★	★		★
Johnson et al. 2016	★			★	★	★	★	★
Wieckowski et al 2017	★	★	★	★		★	★	★

¹ High quality

: ≥ 7★ (Additional requirements: Selection domain 3-4 stars AND Comparability domain 1-2 stars AND Outcome domain 2-3 stars)

² Moderate quality: ≥ 5★ (Additional requirements: selection domain 2 stars AND comparability domain 1-2 stars AND outcome domain 1-3 stars)³ Poor quality: ≤ 4★ (Additional requirements: selection domain 0-1 stars OR comparability domain 0 stars OR outcome domain 0 stars)

Review: Depression & Offspring

Author accepted manuscript

